Drug Toxicities of Common Analgesic Medications in the Emergency Department

Mateusz Ciejka, MD[a], Khoa Nguyen, MD[a],
Martin H. Bluth, MD, PhD[b,c], Elizabeth Dubey, MD[a,*]

KEYWORDS

• Toxicity • Acetaminophen • Opioid • Narcotic • Aspirin • Salicylate
• Emergency department

KEY POINTS

- Acute acetaminophen toxicity is commonly associated with hepatic dysfunction that may not manifest until 24 hours after ingestion; the modified Rumack-Matthews nomogram is used to determine whether treatment with *N*-acetylcysteine is indicated and is based on the serum acetaminophen level beginning at 4 hours after ingestion.
- Acute opioid toxicity is classically characterized by central nervous system depression, respiratory depression, and pupillary constriction; naloxone should be administered to achieve adequate respiration rather than a normal level of consciousness.
- Many opioids have a longer duration of action than naloxone; thus, patients who respond to naloxone should continue to be observed for persistent opioid toxicity.
- Acute aspirin toxicity can present with hyperthermia, altered mental status, coma, pulmonary edema, and shock, which require prompt recognition and initiation of therapy with hydration, sodium bicarbonate administration, electrolyte replacement, and dialysis when indicated.

ACETAMINOPHEN TOXICITY

Background

Acetaminophen was first clinically used in 1955 and since then has become the most commonly used antipyretic and analgesic medication in the United States. Acetaminophen is available as an isolated agent and is a component of prescription and over-the-counter medications used throughout the world. Acetaminophen is safe to administer at standard therapeutic doses, although it has been shown that prolonged use and overdosing of the drug can lead to nonfatal or fatal hepatic injury.[1] In fact,

[a] Department of Emergency Medicine, Wayne State University School of Medicine, 4201 St. Antoine, 6F UHC, Detroit, MI 48201, USA; [b] Department of Pathology, Wayne State University School of Medicine, 540 East Canfield, Detroit, MI 48201, USA; [c] Consolidated Laboratory Management Systems, 24555 Southfield Road, Southfield, MI 48075, USA
* Corresponding author.
E-mail address: edube@med.wayne.edu

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acetaminophen toxicity is the most common cause of acute hepatic failure in the United States.[2]

Pathophysiology

Acetaminophen is typically used for its antipyretic and analgesic properties, although it also has mild anti-inflammatory and antiplatelet functions, which are induced by inhibiting prostaglandin synthesis. Contrary to the mechanism of action of nonsteroidal anti-inflammatory drugs, which inhibit peripheral prostaglandin synthesis through the direct inhibition of prostaglandin E_2 (PGE_2) synthase enzymatic activity via the cyclo-oxygenase (COX) binding site, acetaminophen acts on the peroxidase binding site on PGE_2 and indirectly inhibits COX activation.[3,4]

At therapeutic levels, most circulating acetaminophen is metabolized through conjugation with glucuronide or sulfate moieties, converting it into nontoxic products that are renally excreted.[4–6] However, 5% to 15% of acetaminophen is metabolized by cytochrome (CYP) P450 enzymes into *N*-acetyl-*p*-benzoquinone imine (NAPQI), a hepatotoxic highly reactive metabolite. NAPQI has a short half-life and is rapidly conjugated into nontoxic metabolites with glutathione and other moieties before being renally excreted. At therapeutic doses of acetaminophen, there are sufficient glutathione stores to maintain NAPQI metabolism at an adequate rate, and its nontoxic metabolites are renally excreted.

With excessive NAPQI production or with depletion of glutathione stores, such as in acetaminophen overdose or repeated supratherapeutic dosing, the glucuronidation and sulfation metabolizing pathways are saturated. In turn, additional acetaminophen is metabolized by CYP enzymes to NAPQI. It has been demonstrated that when hepatic glutathione stores are reduced by approximately 70% or more, unmetabolized NAPQI causes hepatotoxicity.[7,8] The reactive molecule covalently binds to hepatic cellular proteins, which leads to hepatocyte necrosis within hours of the drug ingestion.[9]

The current US Food and Drug Administration (FDA)-recommended maximum daily dose of acetaminophen is 4 g in individuals 50 kg and greater and 75 mg/kg in individuals less than 50 kg.[10] According to the FDA, exceeding the maximum recommended daily dose of acetaminophen can cause acute hepatotoxicity, particularly in those individuals with underling liver disease, chronic alcohol use, concomitant treatment with medications that induce CYP enzymes, such as phenytoin and isoniazid, malnutrition, and advanced age.[10–13] Such individuals with increased susceptibility can develop hepatotoxicity at lower doses.

Manifestations of Drug Toxicity

Within the first 24 hours of acetaminophen overdose, most patients will be asymptomatic or have mild nonspecific symptoms, such as nausea, vomiting, and malaise.[14] Laboratory studies are usually normal, and elevated anion gap metabolic acidosis (AGMA) is rare at this stage in massive overdoses.[15] Hepatotoxicity usually will not manifest until 24 hours after ingestion, at which point there may be elevations in transaminase levels (**Table 1**), which may be accompanied by other clinical signs of liver injury, including right upper quadrant abdominal pain or tenderness, liver enlargement, and jaundice. There may also be elevations in prothrombin time (PT) and bilirubin as well as signs of renal function abnormalities. Although with severe toxicity, elevations in transaminases may be seen within the first 24 hours.[6,16] The most severe cases of toxicity involve fulminant liver failure, which can manifest as renal injury, coagulopathy leading to hemorrhage, AGMA, cerebral edema, hepatic encephalopathy, sepsis, and multiorgan failure.[14] Patients who survive this phase generally have resolution of hepatic sequelae, although full histologic resolution may take months.[14]